MEMORANDUM

SUBJECT: Response to Public Comments on the Preliminary Risk Assessments for the Organophosphate Oxydemeton-methyl

FROM: Kathleen Meier, Chemical Review Manager
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TO: OPP Public Docket for Oxydemeton-methyl
Docket number OPP 34167

Introduction

This document addresses public comments that were received in response to EPA's Notice of Availability in the Federal Register (64 FR 1199, January 8, 1999) of preliminary risk assessments for the organophosphate oxydemeton-methyl (ODM). Comments were received from the Registrant, Gowan Company, Henry Hibino Farms, Andrews Seed Company, Mint Industry Research Council, California Agricultural Production Consultants, S & W Seed Company, R-F Seeds, Fifield Land Company, A & J Farms, Middaugh Crop Consulting Service, Grower Shipping Vegetable Association, and 32 individuals who did not specify an affiliation.

It should be noted that many of the comments submitted by Gowan Company, disputed the FQPA 10x Safety Factor, which has since been removed. (See Oxydemeton-methyl Report of the FQPA Safety Factor Committee, July 22, 1999.)

Part I: Response to Comments Received from Gowan Company

A. Response to Gowan Company's Comments on the Health Effects Assessment

1. Comments related to the FQPA 10x Safety Factor

Background: The FQPA Safety Factor Committee, during its evaluation of the hazard and exposure data on June 15 and 16, 1998, recommended that the 10x FQPA safety factor should be retained for ODM because of the concern for heritable effects as demonstrated in an *in vivo* mouse spot test. In addition, there was valid evidence of DNA strand breaks in rat testes cells in an in vitro alkaline elution assay. (See FQPA Safety Factor Recommendations for the Organophosphates, dated August 6, 1998.)

Since the initial FQPA Safety Factor Committee meeting, the Registrant has submitted a toxicokinetic study in the rat. On July 8, 1999, EPA's Hazard Identification and Review Committee (HIARC) evaluated the merit of the toxicokinetic study (MRID 00152368) and the impact of this study on the acceptability of the previously submitted and reviewed *in vivo* alkaline elution assay in the rat (MRID 43776101).

The FQPA Safety Factor Committee met on July 12, 1999 to reevaluate the hazard and exposure data for ODM considering the toxicokinetic study submitted for this organophosphate. Based on these new data, the Committee recommended that the FQPA safety factor (as required by Food Quality Protection Act of August 3, 1996) be removed in assessing the risk posed by ODM.

a. Review of Heritable Effects Studies
   1. *in vivo* studies - germ tissue

Comment: Gowan objects to EPA's conclusion that the *in vivo* rat alkaline elution assay is unacceptable, maintains that this assay should be classified as acceptable. This study was negative for DNA strand breaks in germinal cells but classified unacceptable by EPA, in part, because the exposure time prior to cell harvest was not proven sufficient to detect a positive response.

Response: On July 8, 1999, the HIARC evaluated the merit of a toxicokinetic study in the rat (MRID 00152368), and the impact of this study on the acceptability of a previously submitted and reviewed *in vivo* alkaline elution assay in the rat (MRID 43776101). The alkaline elution assay was previously graded as unacceptable because there was concern that the 4-hour exposure to ODM may not have allowed enough time for sufficient interaction with the target organ (testes). The toxicokinetic study clearly demonstrated that after 4 hours, ODM had enough time to distribute throughout the body, and that the testes were adequately exposed during this time. As there was no longer concern regarding the adequacy of the exposure time in the alkaline elution assay, the HIARC agreed that the *in vivo* alkaline elution assay in the rat was acceptable.

2. *in vivo* studies - somatic tissue

Comments: Gowan has objects to EPA's position regarding the use of the data from the mouse spot test as part of the weight-of-the-evidence for potential heritable effects since the test is performed with somatic cells and not germ cells.

Response: EPA agrees that the target cell in the assay is somatic cells; however, to quote Liane Russell et al. (1981): "While the assay can thus provide a warning of mutagenicity, it should be followed up, whenever possible, with germ-line mutagenesis tests to determine what type of heritable genetic damage (if any) is induced, and in what type of germ cell this induction occurs".

Comments: Gowan claims that HED has ignored the results of other in vivo somatic and germ cell assays. These include the Chinese hamster bone marrow cytogenetic test, the dominant lethal assays and the in vivo alkaline elution assay in rat testes.

Response: Gowan's concerns about EPA's review of the results of other *in vivo* somatic and germ cell assays were expressed prior to the receipt and favorable review of a toxicokinetic study with ODM in the rat. As a result of the new data provided by the toxicokinetic study, the *in vivo* alkaline elution assay was found to be acceptable, and, as a result, the HIARC concluded that the genetic concern resulting from exposure to ODM have been addressed. Further, the requirement for the mouse specific locus test, which evaluates adverse effect on germinal cells, is revoked.

Comments: Gowan objects to the use of published literature in the weight-of-evidence evaluation.

Response: In the interest of public health, EPA can not disregard studies from the open literature that have scientific merit.

Comments: Gowan argues that mortality, severe clinical signs and cytotoxicity that were seen in the mouse spot test are consistent with general toxicity instead of specific genetic toxicity. Gowan also argues that the cytotoxicity (i.e., increased frequency of white mid-ventral spots, WMVS) seen at the high dose indicates that the dose was excessive.

Response: EPA agrees that the high dose (20 mg/kg) was severely toxic to the maternal animals; however, because the mouse spot test is a pre-screen, it has been recommended by Russell et al., (1981) that the assay be carried out at the highest dose that is compatible with survival of the offspring between the time of exposure and observation.

EPA disagrees with Gowan's second argument since the increase in WMVS was not reproducible. In keeping with the precepts of good science, studies are repeated to eliminate biological variation and human error, and only findings that are repeatable are considered valid. Thus, the increased incidence of WMVS, which was only seen in one of the two experiments, is not valid. By contrast, the indicator of mutagenicity (relevant spots, RS) was significantly

increased in both experiments. The data, therefore, indicate that ODM induced a genotoxic and not cytotoxic effect on the target cells in the embryo.

Comments: Gowan objects to EPA's statements regarding the "suggestive evidence of a dose response".

Response: In keeping with the above principle, EPA concedes that the evidence of a dose response is weak and not reproducible.

Comments: Gowan argues that the classification of spots is subjective.

Response: This issue has been discussed by Russell et al., (1980, 1981), and a detailed scoring scheme to distinguish the type of spots has been developed to ensure that scoring is properly done. The laboratory performing the mouse spot test is highly reputable, used the scoring scheme developed by Russell et al., (1981) and conducted the test under GLPs. Furthermore, the performing laboratory was able to reproduce their data which appears to be unlikely if a proper distinction of the types of spots were not made.

Comments: Gowan states that EPA's weight-of-the-evidence conclusion that ODM has the potential to induce heritable effects is "based solely on the suggestion of an effect in somatic cells in the mouse spot test and on lower-tiered in vitro studies" and "is completely inconsistent with EPA's own principles for weighting mutagenicity data." Gowan also disagrees with the conclusions reached in the preliminary risk assessment that the lack of a mouse specific locus test constitutes a data gap for oxydemeton-methyl.

Response: The negative results of the acceptable *in vivo* alkaline elution assay, as well as the negative findings of the dominant lethal assays, lowered the concern for heritable effects from exposure to ODM and obliged the HIARC to revisit the results of the mouse spot test. The primary function of the mouse spot test is as a carcinogenesis screening tool. Although ODM was positive in this test system, it was negative in other *in vivo* assays with somatic cells. In addition, ODM was shown to be non-carcinogenic in CD-1 mice and Fischer 344 rats.

Based on a weight-of-evidence re-evaluation, the HIARC concluded that the genetic concern resulting from exposure to ODM has been addressed. The requirement for the mouse specific locus test, which evaluates adverse effect on germinal cells, is revoked. Therefore, the toxicology database for ODM is now complete.

2. Possible Refinements to the Occupational Risk Assessment

a. Mixer/Loader/Applicator assessments

Background: Dermal and inhalation exposure assessments for occupational handlers involved in mixing/loading and/or applying oxydemeton-methyl were conducted by EPA using a range of

application rates and frequency of use from current product labels, the PHED Version 1.1 database, and standard assumptions regarding average body weight, work day intervals, and daily amount handled (acres treated/day or volume used/day). Aggregate risk indices (ARIs) were used to combine dermal and inhalation MOEs. This index normalizes all uncertainty factors to one; an ARI of less than one is indicative of a risk concern.

Short-Term Risk Summary: When additional PPE is used, combined short-term dermal and inhalation risks are not of concern for the majority of exposure scenarios (ARIs range from 1.1 to 13). However, there are two scenarios where engineering controls are necessary to mitigate risk concerns (ARIs 0.55-0.7); these are applications using an airblast sprayer at a rate of 1.13 lb ai/A and mixing/loading for aerial/chemigation application at the rates of 0.75 and 1.0 lb ai/A. In addition, there are four scenarios where risks are of concern and engineering controls are not feasible (ARIs range from 0.0079 to 0.36); these are applying liquids using a high pressure handwand, mixing/loading/applying liquids using a paint brush (for tree bark treatment), backpack sprayer/knapsack, and a low pressure handwand.

Intermediate-Term Risk Summary: When additional PPE is used, combined intermediate-term dermal and inhalation risks are of concern for all 13 major exposure scenarios (ARIs range from 0.00048 to 0.82). Using engineering controls where feasible, intermediate-term ARIs are >1 for only five scenarios; for two of these, only the lower application rates (0.38 to 0.5 lb ai/A) yield ARIs >1. Intermediate-term risk estimates for all other scenarios with maximum engineering controls exceed EPA's level of concern (ARIs range from 0.07 to 0.95).

Comments: Gowan believes that EPA has conducted a high-end "Tier I type" estimate of handler risk by utilizing "default" maximum point estimate assumptions for exposure parameter inputs. They do not object to HED's assessment of short-term risks because it is their understanding that the major uses pass the "Tier I type" screen, yielding acceptable ARIs with minimal personal protective equipment. To address refined input parameters for intermediate-term handler risk assessment, Gowan has submitted information on the distribution of application rates and acres treated for major oxydemeton-methyl uses.

Response: EPA recognizes that the current intermediate-term handler assessment utilizes point estimate assumptions, but does not fully agree that all of the input parameters are "high-end approximations of exposure and risk." Gowan's submission "Preliminary Evaluation of Handler Exposure to Oxydemeton-methyl" (MRID 44783101) has been reviewed by EPA. An evaluation of this submission, and the survey data therein, supporting the use of application rates and acres treated as a distribution, is provided in a separate memorandum (from K. O'Rourke, HED to K. Meier, SRRD, November 2, 1999). EPA's final Risk Assessment for Oxydemeton-methyl has been revised to include the application rate data, as a point estimate, for cole crops. The ARIs presented in the previous risk summary reflect this revision. Regarding the short-term handler assessment, EPA notes that Gowan's conclusion "the major uses have acceptable ARI at the baseline scenario..." does not apply to the scenarios for hand-held equipment and application by airblast. While these scenarios may not be considered major uses, they still exist and are of risk

concern to EPA.

b. Reentry Assessments

Background: EPA conducted postapplication exposure assessments and calculated restricted entry intervals (REIs) using Gowan's ODM-specific dislodgeable foliar residue data for cauliflower, cotton, bell pepper, and sugar beets, and standard transfer coefficients.

Comments: Gowan would prefer that the Agency postpone its postapplication assessment until data are available from the Agricultural Reentry Task Force (ARTF). Gowan is concerned that basing risk mitigation options on default assumptions is unfair to registrants of organophosphate pesticides. Gowan has submitted a "higher tiered" postapplication exposure assessment.

Response: EPA used Gowan's own study data to estimate the dislodgeable foliar residues (DFRs) rather than the standard assumptions of twenty percent initially available and ten percent dissipation per day. EPA believes the use of Gowan's DFR data was reasonable and realistic. DFR data for cauliflower, cotton, bell peppers, and sugar beets were used to calculate an average (rather than maximum) initial DFR value and a dissipation rate. A generic DFR dissipation curve was developed from these average values for crops that were not included in the study. The data that the ARTF will eventually provide are related to transfer coefficients; this is the portion of the exposure algorithm in which EPA used standard values. Although precise transfer coefficients are not currently available from the ARTF, the standard values used by HED (1,000, 2,500, 4,000 and 10,000 cm^2/hr) to represent the various activities associated with a wide variety of crops, are well within the range expected by members of the ARTF. The restricted entry intervals (REIs) calculated by EPA range from 5 days to 59 days depending on the crops and their associated activities.

Gowan's submission "Preliminary Evaluation of Oxydemeton-methyl Dislodgeable Foliar Residues and Reentry Intervals: Conventional and Monte Carlo Assessments" (MRID 44806801) has been reviewed by EPA. An evaluation of this submission is provided in a separate memorandum (from K. O'Rourke, HED to K. Meier, SRRD, November 3, 1999). The information provided in the submission did not warrant changes to EPA's Revised Risk Assessment for Oxydemeton-methyl, however, the assessment has been revised to further delineate predicted REIs based on crop and activity groupings.

B. Response to Gowan Company's Comments on the Ecological Fate and Effects Assessment

Comment: Gowan disagrees that there is a chronic exposure concern to birds. To refute an adverse effect of ODM on bobwhite reproduction, Gowan compares treated groups from ODM to an artificial control group, formed by merging the control group from the ODM study with control groups from 4 other bobwhite reproduction studies conducted in the same facility. They

claim that there is no statistically significant difference in 14 day old hatchling weights at any dose level

Response: EPA does not regard the procedure of combining control groups from multiple studies as appropriate, and has rejected this approach for assessments of other chemicals. The NOAEC and LOAEC should be determined by comparing groups formed by random assignment of test animals to treatment levels in a single study. However if there is concern related to the possibility of abnormal outcomes for the ODM control group, it may be useful to compare the ODM controls to historical controls and determine if the ODM controls are representative for the testing facility.

Comment: Gowan argues that EPA's exposure analysis is a lower-tier screen, and a more refined exposure assessment can be based on data from Magnitude of Residue (MOR) studies. Gowan Co. proposes (1) that EPA should rely on data from certain MOR studies; and (2) that the NOAEC should be compared to an average exposure level calculated by averaging over localities.

Response: While the concentrations reported in these data are somewhat lower than those used in EPA's standard procedure, the information still would not refute an avian reproductive concern. MOR data might be useful as supplemental information. Based on discussions with HED staff, we understand that the MOR data are based on blended samples in order to be useful for assessment of human dietary exposure. The residue available to wildlife would be primarily on plant or other surfaces. Therefore, to the extent that the blending process is appropriate for human dietary exposure assessment, the process can lead to underestimation of residue available to wildlife. This may be particularly true for cole crops which would have a relatively low ratio of surface area to human-edible mass. These types of factors need to be investigated when residue information is submitted for use in wildlife exposure assessment, from studies (such as MOR studies) not actually designed for wildlife exposure assessment. As far as EFED can tell, the MOR data are roughly consistent with the data we routinely use given differences in the collection of samples. MOR data do not quantify the residue falling on the ground or available on seeds or insects, nor do they necessarily reflect residues immediately after application. The role of residues on plant surface, versus residue on other media, would depend on the foraging behavior of various receptor species.

Comment: Gowan responds to an EPA argument (in the Dec. 22 1998 memo) that the MOR data would not refute the concern if it were used. Gowan describes EPA's argument as relying on a concentration (20 ppm) that is "worst case, infrequent and extreme."

Response: With regard to the possibility of a more "probabilistic" assessment we caution that an EPA "concern" would not necessarily be refuted by showing that exposure levels will reach ecologically damaging levels in only a small percentage of localities and/or periods. For any pesticide, EPA will be concerned with the possibility of localized adverse effects, particularly given that some species or ecosystem types may actually be localized. We note that an average

residue measurement, as suggested by Gowan, would be exceeded for about half of localities.

Comment: Gowan Co. points out that exposures off-site, resulting from drift as evaluated using the "AGDRIFT" model, would be lower than values on the crop resulting from direct application.

Response: The AGDRIFT model is the property of the Spraydrift Task Force, a coalition of pesticide registrants, although Agency staff have participated in the development of the spraydrift database and model. Use of the model for ecological exposure assessment is under review by EPA.

Part II: Response to Comments from the Public

The Agency received many generic comments from the agricultural community; grower groups, seed producers, agronomists, and pest control advisors. Many of the comments were similar in nature. To avoid redundancy, EPA responses have been grouped in the six categories listed below.

A. Comments Regarding Worker Exposure of ODM

Comment: Metasystox-R (MSR), an end-use product of ODM, is only applied using a closed mixing and loading system for alfalfa and sugarbeets specifically. Due to the careful training and extreme caution taken in the use of MSR, it is a very safe chemical.

Response: For many applications, including alfalfa and sugarbeet, the label does require that Metasystox-R is applied using chemigation, which means that a closed mixing and loading system must be used. Even with closed mixing and loading systems, monitoring data have shown that some exposure to workers occurs. According to the current risk assessment, chemigation exposure scenarios, even with maximum engineering controls have risks of concern for intermediate-term dermal exposure. The Aggregate Risk Index (ARI) for dermal is 0.07 - 0.19, where an ARI of 1 would be considered adequate. Due to the method of application, there is no applicator risk, however, for most crops there would be concerns for workers reentering treated fields.

B. Comments Related to Additional Data, Data-Call-Ins, and Default Assumptions

Comment: Many commentors stated that data from the Agricultural Reentry Task Force (ARTF) and Market Basket Survey is currently being developed and should be used in the risk assessment. This data would be preferable to the data that the Agency has been using because it is based on actual rather than theoretical risk. The Agency should refrain from making any final decision until the new data are available. A common theme was that EPA should use actual data, particularly usage data, and avoid default assumptions in its assessments.

Response: In phase four of reregistration, EPA exercised its data call-in authority to require studies to upgrade chemical databases to current scientific standards. Most of the OPs were subject to reregistration DCIs and registrants have been allowed ample time to submit those studies. EPA makes its reregistration and tolerance reassessment decisions on the best data that are available. Where data are incomplete EPA may compensate by using an additional uncertainty factor or by making a reasonable health-protective assumption. This has long been EPA practice, and is reinforced by FQPA's emphasis on the importance of the use of uncertainty factors where data are incomplete.

Specifically, in the case of ODM, it should be noted that dietary (both food and drinking water) are not of concern for ODM alone. Actual residue monitoring data, where available, were used to calculate dietary risk. Data from the ongoing Market Basket Survey, are likely to be available early in 2000, and could possibly be used to further refine ODM (and other chemical) residue estimates prior to the cumulative assessment of OPs. Regarding ARTF data, the registrant has already submitted ODM-specific DFR data, which were used to develop the REIs. It is true that the transfer coefficients (TC) used in the ODM assessment are standard values based on historical data and may be refined based on ARTF data. Preliminary reports from theTask Force indicate that the standard values currently used are relatively realistic.

For a discussion of the sources of use and usage data and how EPA employs these data in its assessments, the reader is referred to a science policy paper entitled, "The Role of Use-Related Information in Pesticide Risk Assessment and Risk Management," which is currently available on EPA's web site: http://www.epa.gov/pesticides/op/ .

C. Comments Related to Dietary Risk

Comment: Alfalfa grown for seed should not be included in the dietary risk equation.

Response: The ODM Federal label currently allows alfalfa chaff to be used for feed for livestock, thus ODM treated alfalfa could be a contributor, albeit minor, to the dietary risk from meat and milk. However, in the ODM assessment, the contribution was negligible.

D. Testimonial Comments

Comment: Many commentors claimed that there are no equivalent alternatives available and that some alternatives would result in more pesticide being used.

Response: EPA will consider these factors, as appropriate, in our risk management decisions. Specifically, under FQPA, EPA cannot use the biological or economic importance of a chemical as a factor in determining allowable dietary risk. However, if risk management is necessary, these factors would be considered in determining which chemical uses are most critical and should be

retained.

E. Comments Related to the Role of OPs in Integrated Pest Management (IPM)

Comment: Many comments noted that ODM fits well into growers established IPM programs to minimize pest resistance. The loss of ODM would reduce effectiveness of entire IPM programs. ODM is essential to alfalfa grown for seed and sugarbeets. The loss of any tool in the IPM arsenal can result in the return to prophylactic use of pesticides.

Response: EPA recognizes the importance of some OPs in IPM and resistance management programs. We intend to consider these factors, as appropriate, in our risk management decisions. Specifically, under FQPA, EPA cannot use the biological or economic importance of a chemical as a factor in determining allowable dietary risk. However, if risk management is necessary, these factors would be considered in determining which chemical uses are most critical and should be retained.

F. Comments from Universities and Extension Services

Comment: Ben Simko, Agricultural Extension Agent and Professor, Crop and Soil Science Department of Oregon State University, Malheur County Extension Office of Ontario, Oregon, Lynelle Drake, Andrews Seed Company, and Northwest Alfalfa Seed Growers Association submitted a very thorough benefit/use profile of oxydemeton-methyl on alfalfa.

Response: The information provided in numerous comments pertaining to alfalfa grown for seed has been reviewed. The Biological Economic Analysis Division (BEAD) concurs with the comments as to the importance of oxydemeton-methyl for alfalfa. ODM not only provides control of two of the most important pests of this crop but through its systemic activity and night application it minimizes impact on cutter bees which are important pollinators of alfalfa. Use of other chemicals would disrupt this program.